Phase II Randomized Study of Vandetanib Plus Gemcitabine or Gemcitabine Plus Placebo as First-Line Treatment of Advanced Non–Small-Cell Lung Cancer in Elderly Patients

Cesare Gridelli, MD, Silvia Novello, MD,† Nicoletta Zilembo, MD,‡ Andrea Luciani, MD,§ Adolfo Gino Favaretto, MD,‖ Filippo De Marinis, MD,¶ Giovenzio Genestreti, MD,# Lucio Crinò, MD,** Francesco Grossi, MD,†† Orazio Caffo, MD,‡‡ Francesco Ferraù, MD,§§ Giorgio Cruciani, MD,‖‖ Alba Ariela Brandes, MD,¶¶ Domenico Galetta, MD,## Sandro Barni, MD,*** Gianpiero Fasola, MD,††† Giulio Cerea, MD,‡‡‡ Silvia Ferrari, MD,§§§ Claudio Iannacone, MSc,‖‖‖ and Fortunato Ciardiello, MD¶¶¶*

Introduction: The aim of the present study was to evaluate the efficacy and tolerability of vandetanib plus gemcitabine (V/G) compared with gemcitabine alone in elderly patients with untreated advanced non–small-cell lung cancer.

Methods: This was a phase II, randomized, double-blind study. A total of 124 elderly patients (mean age, 75 yr; age range, 70–84 yr; 73% men) received V/G (n = 61) or placebo plus gemcitabine (n = 63). Progression-free survival (PFS) was the primary endpoint. Secondary endpoints were overall survival, objective response rate, duration of response, disease control rate, time to deterioration of performance status, and safety outcomes.

Results: PFS was significantly prolonged with V/G (median, 183 days; 95% confidence interval, 116–214) compared with placebo plus gemcitabine (median, 169 days; 95% confidence interval, 95–194; p = 0.047). No statistically significant differences between arms were observed in all secondary endpoints, including overall survival. The addition of vandetanib to gemcitabine was well tolerated. The rate of patients with ≥1 treatment-related adverse event was comparable in the two arms, pyrexia, dyspnea, and neutropenia being the most common adverse events.

Conclusions: V/G combination was associated with a statistically significant prolongation of PFS compared with gemcitabine alone in untreated elderly patients with advanced non–small-cell lung cancer, with an acceptable safety profile.

Key Words: Vandetanib, Gemcitabine, Non–small-cell lung cancer, Elderly.

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*Division of Medical Oncology, "SG Moscati" Hospital, Avellino, Italy; †Department of Oncology, University of Turin, AOU San Luigi Orbassano, Turin, Italy; ‡Medical Oncology 1, "Fondazione IRCCS Istituto Nazionale dei Tumori", Milan, Italy; §Department of Oncology, San Paolo Hospital, Milan, Italy; ‖Second Medical Oncology Unit, "Istituto Oncologico Veneto", Padua, Italy; ¶European Institute of Oncology, Milan, Italy; #Department of Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola (FC), Italy; **Division of Medical Oncology, S. Maria della Misericordia Hospital, Perugia, Italy; ††Lung Cancer Unit, National Institute for Cancer Research, Genoa, Italy; ‡‡Medical Oncology Department, Santa Chiara Hospital, Trento, Italy; §§Medical Oncology Unit, San Vincenzo Hospital, Taormina, Catania, Italy; ‖‖Oncology Unit, Santa Maria delle Croci Hospital, Ravenna, Italy; ¶¶Medical Oncology Department, AUSL Bologna, Italy; ##Medical Oncology Unit, "Giovanni Paolo II" National Cancer Centre, Bari, Italy; ***Department of Oncology, Azienda Ospedaliera Treviglio, Treviglio (BG), Italy; †††Department of Oncology, University Hospital of Udine, Udine, Italy; ‡‡‡Department of Oncology, Ospedale Niguarda Ca' Granda, Milan, Italy; §§§AstraZeneca, Basiglio (MI), Italy; ‖‖‖LB Research, Cantù (CO), Italy; and ¶¶¶Medical Oncology, Second University of Naples, Naples, Italy.

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Address for correspondence: Cesare Gridelli, MD, U.O. Oncologia Medica, A.O. "S.G. Moscati", Contrada Amoretta, 83100 Avellino, Italy. E-mail: cgridelli@libero.it

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Vandetanib is a novel small-molecule tyrosine kinase (TK) inhibitor with antiepidermal growth factor receptor, antivascular endothelial growth factor receptor-2, and anti-rearranged during transfection TK activity.[1] In pretreated non–small-cell lung cancer (NSCLC) patients, vandetanib monotherapy did not show an overall survival (OS) advantage when compared with placebo[2] and had a similar progression-free survival (PFS) when compared with erlotinib.[3] Vandetanib showed a slight improvement in PFS when administered in association with docetaxel versus docetaxel alone[4] and a trend to improved PFS with the combination vandetanib plus pemetrexed versus pemetrexed alone.[5] However, both trials resulted in improved lung cancer symptom control.

Although there is evidence that a platinum-based doublet may be effective,[6] single-agent chemotherapy with a

third-generation drug (e.g., vinorelbine, gemcitabine, or taxane) was, at the time of the start of study, a recommended option for unselected elderly patients with advanced NSCLC.[7] A recently published meta-analysis on benefit-to-risk ratio of doublets in advanced NSCLC concluded that combination platinum-based therapy in NSCLC patients more than 70 years old may be more favorable than single agents on overall response rate (ORR), but not on OS.[8]

This phase II randomized, double-blind, placebo-controlled study was designed to determine whether the addition of vandetanib to gemcitabine, in comparison to gemcitabine as single agent, significantly prolongs PFS in untreated elderly patients with advanced NSCLC.

METHODS

This study included patients aged ≥70 years with confirmed stage IIIB/IV NSCLC (according to UICC TNM Classification of Malignant Tumours, 6th edition), anticancer therapy naïve, WHO PS (World Health Organization-performance status) of 0–2, measurable disease according to Response Evaluation Criteria in Solid Tumors, life expectancy ≥12 weeks, and no significant hematologic, hepatic, renal, or cardiac abnormalities. Patients with brain metastases were eligible if they had not received treatment within the 4 weeks before entry and stable without steroid treatment for 10 days. Patients receiving any treatment known to have an effect on NSCLC (except palliative radiotherapy and bisphosphonates for bone metastases) within 4 weeks before the start of study were excluded.

Written informed consent was obtained from each participant. The study was approved by the Ethics Committee of each site.

Eligible patients were randomized 1:1 to receive vandetanib plus gemcitabine (V/G) or placebo plus gemcitabine (P/G). The computer-generated randomization scheme was strictly sequential with blocks of randomization codes being sent to each center according to the recruitment potential.

Vandetanib or placebo was administered as single oral 100 mg daily doses. Gemcitabine was administered at a 1200 mg/m^2 dose as an intravenous infusion on day 1 and day 8 of each 21-day cycle (maximum 6). Treatment was discontinued once a patient experienced disease progression or a ≥3 grade toxicity.

Radiological evaluation using RECIST 1.0 was performed at baseline and every 6 weeks until progression.

Primary endpoint of the study was PFS. Secondary endpoints were OS; ORR (complete response or partial response); duration of response; disease control rate (percentage of patients with complete response or partial response or stable disease

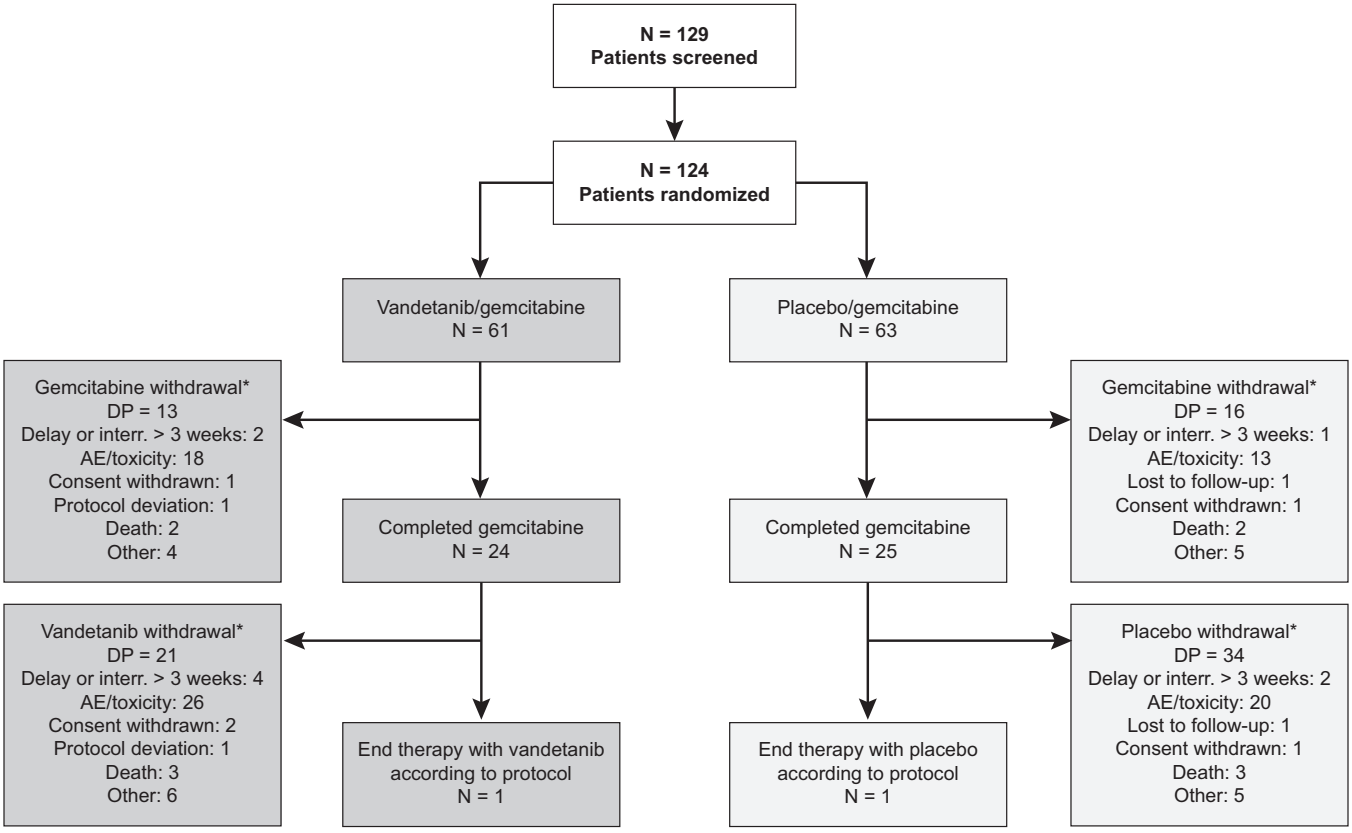

FIGURE 1. Disposition of patients and reasons for withdrawal. *Patients may have more than one reason for withdrawal. AE, adverse event; DP, disease progression.

≥6 wk); and time to deterioration of performance status (TDPS, the time from randomization to a change from baseline ≥1).

Safety analyses included adverse events (AEs), laboratory parameters, vital signs, and electrocardiogram.

Assuming a median PFS of 3 months for gemcitabine,[9] a minimum of 122 patients (61 per arm) were planned to detect a 50% prolongation with V/G (median PFS of 4.5 months), assuming an accrual period of 12 months, a maximum follow-up time of 20 months, and no drop-outs. For this comparison, 110 progression events were required.

In the PFS analysis, survival curves, medians, and their 95% confidence intervals (CIs) were estimated applying the Kaplan-Meier method. The log-rank test was used to compare PFS outcomes. The Cox's proportional hazard regression model was used to analyze covariates of interest (tumor stage, number of organs involved, prior adjuvant chemotherapy, histology, smoking history, gender, QTc prolongation, and tumor response).

Time-dependent variables (OS, duration of response, and TDPS) were analyzed like PFS. The comparison between groups in ORR, disease control rate, and proportion of patients alive at 1-year postrandomization was performed by chi-square test.

AEs were classified by primary system organ class according to the MedDRA thesaurus version 12. For continuous variables, the change from baseline to each postbaseline visit was calculated.

RESULTS

This study was conducted from October 2008 to December 2011 in 17 sites in Italy. Figure 1 shows the disposition of patients and reasons for withdrawal. Demographic and other baseline characteristics were comparable in the two arms (Table 1).

The median number of cycles of gemcitabine infusions was 4 (range, 1–6) in both arms, with a similar percentage of patients receiving the complete scheme of gemcitabine (40% for each arm). The median exposure was 78.5 days (range, 1–528) in the V/G arm and 91 days (range, 1–441) in the P/G arm.

Table 2 summarizes efficacy results. Median PFS (Figure 2) was significantly prolonged in the V/G arm (183 days; 95% CI, 116–214) compared with the P/G arm (169 days; 95% CI: 95–194; $p = 0.047$). In the V/G arm, 10 patients (16.4%) were censored and 51 failed treatment, whereas five patients (7.9%) were censored and 58 failed in the P/G arm. The adjusted Cox regression analysis on PFS showed that only sex had a statistically significant effect (hazard ratio of female patients versus male patients: 0.63; 95% CI, 0.40–0.99; $p = 0.043$). The explorative analysis showed that median PFS was significantly prolonged in the V/G arm compared with the P/G arm for the following covariates: patients with all combined types of histological tumors except squamous cell carcinoma (V/G arm: 196 days; 95% CI, 160–245; P/G arm: 162 days; 95% CI, 87–191; $p = 0.008$); never/past smokers (V/G arm: 188 days; 95% CI, 129–236; P/G arm: 169 days; 95% CI, 99–194; $p = 0.048$); and female patients (V/G arm: 245 days; 95% CI, 175–693; P/G arm: 91.5 days; 95% CI, 45–224; $p = 0.010$).

TABLE 1. Summary of Demographic and Other Baseline Characteristics and of Tumor History

	Vandetanib/ Gemcitabine	Placebo/ Gemcitabine
	n = 61	*n* = 63
Sex, *n* (%)		
Males	45 (73.8)	45 (71.4)
Females	16 (26.2)	18 (28.6)
Age (yr), mean (range)	75.03 (70–82)	75.48 (70–84)
WHO PS, *n* (%)		
Grade 0	33 (54.1)	38 (60.3)
Grade 1	27 (44.3)	24 (38.1)
Grade 2	1 (1.6)	1 (1.6)
Smoking history, *n* (%)		
Never smoked	8 (13.1)	13 (20.6)
Current smokers	15 (24.6)	16 (25.4)
Past smokers	37 (60.7)	34 (54.0)
Missing	1 (1.6)	—
Previous radiotherapy, *n* (%)	13 (21.3)	8 (12.7)
Type of tumor, *n* (%)		
Squamous cell carcinoma	13 (21.3)	17 (27.0)
Adenocarcinoma	31 (50.8)	41 (65.1)
Bronchoalveolar carcinoma	3 (4.9)	1 (1.6)
Large cell carcinoma	2 (3.3)	—
Other or missing	12 (19.6)	4 (6.3)
Grade of histopathological diagnosis, *n* (%)		
Well differentiated (grade 1)	4 (11.4)	—
Moderately differentiated (grade 2)	4 (11.4)	4 (12.1)
Poorly differentiated (grade 3)	8 (22.9)	11 (33.3)
Unknown or missing	19 (54.3)	18 (54.6)
Stage at study entry, *n* (%)		
IIIB (supraclavicular lymph node metastases)	6 (9.8)	7 (11.1)
IV	55 (90.2)	56 (88.9)

WHO PS, World Health Organization performance status.

In the V/G arm, 37 patients (60.7%) had no World Health Organization-performance status increase from baseline and 24 (39.3%) had ≥1 point increase compared with 31 patients (49.2%) with no increase and 32 (50.8%) with deterioration in the P/G arm.

The rate of patients with at least one AE was 96.7% and 98.4% for arm V/G and P/G, respectively. Serious AEs were reported in 42.6% in arm V/G and 32.7% in arm P/G.

Ten patients (16.4%) in arm V/G and eight (12.7%) in arm P/G died, mostly for disease progression. Dose adjustment, temporary interruption, or permanent discontinuation of study drug was required in 72.1% of V/G and 60.3% of P/G. Grade IV toxicities were reported in five patients (8.2%) in the V/G arm and in five (7.9%) in the P/G arm. Table 3 shows the most common AEs. Five patients (8.2%) in the V/G arm and two (3.2%) in the P/G arm had at least one QTc interval prolongation during the study.

TABLE 2. Summary of Results of Efficacy

	Vandetanib/Gemcitabine	Placebo/Gemcitabine	
	***n* = 61**	***n* = 63**	***p*[a]**
PFS (days), median (95% CI)	183 (116–214)	169 (95–194)	0.047
OS (days), median (95% CI)	262 (170–245)	305 (213–355)	0.896
Alive at one year, *n* (%)	19 (31.1)	19 (30.2)	0.90
Objective response, *n* (%)	9 (14.8)	8 (12.7)	0.74
DOR (days), median (95% CI)	225 (175–0)	214 (124–232)	0.162
Disease control, *n* (%)	44 (72.1)	42 (66.7)	0.51
TDPS (days), median (95% CI)	167 (64–0)	111 (79–188)	0.659

[a]Log-tank test in survival function data and chi-square test in proportions.
PFS, progression-free survival; CI, confidence interval; OS, overall survival; DOR, duration of response; TDPS, time to deterioration of performance status.

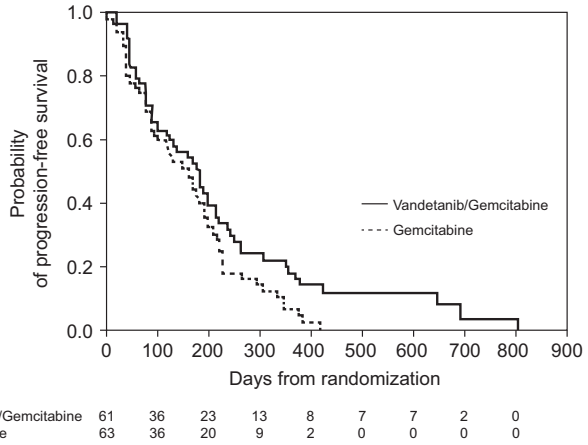

FIGURE 2. Progression-free survival: Kaplan-Meier estimate of survival distribution function—unadjusted.

DISCUSSION

This study compared the efficacy and tolerability of treatment with vandetanib given in addition to gemcitabine versus gemcitabine plus placebo in 124 untreated elderly patients with advanced NSCLC and satisfactory health status and organ function.

The two treatment groups were balanced in terms of demographic and baseline characteristics, including tumor staging and prognostic factors. Results of the primary endpoint showed that PFS was significantly prolonged in the V/G arm compared with P/G. The significant benefit in the V/G group was obtained despite the PFS in the control group was longer than expected.[9] However, our assumption of a 50% PFS prolongation was not reached.

The preplanned subgroups' explorative analysis showed that PFS was significantly prolonged with V/G compared with P/G alone in patients with all types of histological tumors except squamous cell carcinoma, in never/past smokers and in female patients. However, it should be noted that the subpopulations, in which a statistically significant difference between arms was not observed, included a limited number of patients, which were likely not adequately powered for a reliable comparison between arms. Of all secondary endpoints,

TABLE 3. Most Common AEs of Any Grade (i.e., Reported in ≥10% of Patients in Either Arm) and of Grade ≥3 (i.e., Reported in ≥2% of Patients in Either Arm)

	Vandetanib/ Gemcitabine	Placebo/ Gemcitabine
	***n* = 61**	***n* = 63**
AEs of any grade		
Pyrexia	17 (27.9)	17 (27.0)
Dyspnea	13 (21.3)	19 (30.2)
Neutropenia	17 (27.9)	14 (22.2)
Fatigue	14 (23.0)	15 (23.8)
Thrombocytopenia	14 (23.0)	13 (20.6)
Anorexia	8 (13.1)	17 (27.0)
Asthenia	9 (14.8)	13 (20.6)
Rash	15 (24.6)	5 (7.9)
Anemia	8 (13.1)	14 (22.2)
Diarrhea	9 (14.8)	9 (14.3)
Cough	9 (14.8)	10 (15.9)
Nausea	7 (11.5)	8 (12.7)
Edema peripheral	4 (6.6)	12 (19.0)
Chest pain	2 (3.3)	12 (23.8)
Vomiting	4 (6.6)	7 (11.1)
Hypokalemia	3 (4.9)	8 (12.7)
Grade ≥3 AEs[a]		
Neutropenia	7 (11.5)	8 (12.7)
Dyspnea	5 (8.2)	7 (11.1)
Fatigue	4 (6.6)	3 (4.8)
Anemia	3 (4.9)	2 (3.2)
Thrombocytopenia	4 (6.6)	2 (3.2)
Pulmonary embolism	3 (4.9)	3 (4.8)
Pneumonia	2 (3.3)	—
Pulmonary edema	3 (4.9)	—
Respiratory failure	1 (1.6)	2 (3.2)
Asthenia	—	2 (3.2)
Rash	2 (3.3)	—
Cerebral ischemia	—	2 (3.2)

Data are number (%) of patients.
[a]According to the NCI CTCAE, Version 3.0.
AE, adverse event.

no statistically significant differences were found, including tumor response and survival.

The addition of vandetanib to gemcitabine was associated with a satisfactory toxicity profile. Pyrexia, dyspnea, and neutropenia were the most common AEs and were observed in comparable rates in the two arms, being neutropenia and pyrexia the results of gemcitabine-induced myelosuppression and dyspnea a disease-related symptom.

Among the other most common AEs related to vandetanib, the incidence of diarrhea was comparable in the two treatment arms, whereas skin rash was more frequent in patients in the V/G arm than in the P/G arm. In the present study, vandetanib may have caused rash in a lower proportion of patients than that previously reported.[10] Among the cardiovascular side effects, less than 10% of patients treated with vandetanib reported increased blood pressure, with no cases of grade III–IV hypertension in either arm, and none of the patients with blood pressure elevation required treatment discontinuation, interruption, or delay due to this event. QT interval prolongation has also been reported in clinical trials with vandetanib,[11] particularly in view of the long terminal elimination half-life of the drug.[12] In this study, a QTc interval prolongation was reported in five patients treated with vandetanib and in two in the control group. However, this event was not associated with an increase in risk of serious cardiac events in the V/G arm.

To our knowledge, this is the first study conducted in elderly patients with vandetanib and the first evidence of its combination with gemcitabine. Consistent with previous trials,[13] an improvement in PFS in the vandetanib arm did not translate into an improvement in OS. However, the group of patients who received vandetanib in this and in previous trials experienced a delay in TDPS, suggesting palliative benefits.

Taking into account the results of this phase II study in terms of efficacy and safety, further research is of interest to better identify the group of patients who might benefit from vandetanib treatment.

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